In the Claims (Marked-Up Version)

Please cancel claim 10 without prejudice, as drawn to a non-elected invention.

1. (Four Times Amended) An isolated and purified bacterial reverse transcriptase (RT) of (SEQ ID. 1), or a substantially homologous amino acid sequence which synthesizes msDNA~~, which is essential for the synthesis of msDNA *in vivo*~~, and which RT further comprises a sequence of amino acid residues as follows: Tyr-Xaa_6-Asp-Asp (SEQ ID No:50), wherein Xaa_6 is alanine or cysteine and further ~~comprising~~ comprises a sequence of amino acid residues as follows: Asn-Xaa_1-Xaa_2, wherein Xaa_1 is a hydrophobic residue selected from the group consisting of alanine, leucine, and phenylalanine, and Xaa_2 is a hydrophobic residue selected from the group consisting of leucine, valine, and isoleucine.

7. (Four Times Amended) An isolated and purified bacterial reverse transcriptase (RT) which synthesizes msDNA and which is essential for the synthesis of msDNA *in vivo*, said RT ~~comprising~~ comprises a sequence of amino acid residues as follows: Tyr-Xaa_6-Asp-Asp, wherein Xaa_6 is alanine or cysteine, as shown in SEQ ID No:50, wherein said sequence is located in subdomain 5 shown in Fig. 14 at positions 175-191 of SEQ ID No:32, at positions 175-191 of SEQ ID No:33, at positions 175-191 of SEQ ID No: 34, at positions 168-184 of SEQ ID No: 35, at positions 159-175 of SEQ ID No:36, at positions 171-187 of SEQ ID No:37, and at positions 157-173 of SEQ ID No:38, and further comprising the 61 amino acid residues as shown by black dots in Figure 14 of SEQ ID NOs:32-28, wherein h is a hydrophobic residue and p is a small polar residue.

12. (Four Times Amended) The isolated and purified RT of claim 4 which RT has in the following order starting from the N- to the C-terminus:

(1) an amino acid sequence of Ser-Xaa_3-Xaa_4-Xaa_5 (SEQ ID No: 51), wherein Xaa_3 is a hydrophobic residue selected from the group consisting of valine, phenylalanine, leucine, and isoleucine, Xaa_4 is a polar residue selected from the group consisting of threonine, asparagine, lysine, and serine, and Xaa_5 is a hydrophobic residue selected from the group consisting of tryptophan, phenylalanine, and alanine;

(2) an amino acid sequence of Asn-Xaa_1-Xaa_2, where Xaa_1 is a hydrophobic residue selected from the group consisting of alanine, leucine, and phenylalanine, and Xaa_2 is a hydrophobic residue selected from the group consisting of leucine, valine, and isoleucine;

(3) an amino acid sequence Tyr-Xaa_6-Asp-Asp (SEQ ID No: 50) wherein Xaa_6 is alanine or cysteine; and

(4) an amino acid, ~~sequence~~ Xaa_7, where Xaa_7 is a polar residue selected from the group consisting of arginine, lysine, glutamic acid, glutamine, and valine.

Remarks

Applicants respectfully traverse the withdrawal of Claim 10 from consideration, and submit that Claim 10 is drawn to the same field of invention as the claims currently examined. Applicants submit the product is a reverse transcriptase extension which is limited to use in *in vitro* screening for determining the presence or absence of msDNA in bacterium. Nevertheless, applicants have cancelled claim 10 without prejudice as drawn to a non-elected invention.

Applicants have amended the specification to clarify the recitation to the references "Sun et al." and "Herzer et al. 1992" to show the exact citation of the aforementioned references. Applicants note the confusion to the recitation "Hsu et al. J. Bac., 174 (7): 2384-2387, April 1992b." Generally, the "b" would indicate the second-listed HSU reference from that year. However, Applicants have no specific knowledge as to whether "b" has significance in the citation, but suspect it has no such other significance.

Turning now to the Examiner's objections to newly amended Claim 1, the Applicants have amended the claim according to the Examiner's helpful suggestions to use the word "comprises" to maintain consistency within the claim. Applicant has also amended Claim 7 to change "comprising" to "comprises" to maintain consistency within Claim 7.

Rejections Under 35 U.S.C. §112

Applicants note with appreciation the Examiner's helpful comments with regard to Claim 12, and as a result, have amended the claim to reflect that amino acid Xaa_7 is a polar residue rather than a sequence.

Turning now to the Examiner's rejections under the first paragraph of 35 U.S.C. §112, the Applicants have amended Claim 1 to claim the reverse transcriptase of (SEQ ID NO:1 or a substantially homologous amino acid sequence). Support for this amendment may be found on page 15 of the Applicants' specification and the sequence listing submitted by the Applicant which provides that SEQ ID NO:1 is a 485 amino acid residue sequence. As a result of the amendment to Claim 1, and the resulting effect on related Claims 2, 4-6, 12 and 17, the Applicants submit that the claims provide an adequate structural description of reverse transcriptase. Further, the Applicants submit that Claim 15 provides more than a mere recitation of a 4- or 5-amino acid motif. Specifically, Claim 15 provides that the claimed reverse transcriptases must have a YX DD box along with an amino acid sequence Asn-Xaa_1- Asn-Xaa_2, wherein Xaa_1- Xaa_2 are hydrophobic residues. Given the specificity of interaction between hydrophobic residues along with the particular interaction of triocine X aspiratic acid, one skilled in the art would recognize Applicants' were in possession of the claimed genus of Claim 15 and its resulting dependent Claim 16. This combination allows for a different amino acid sequence of which one skilled in the art could readily ascertain

Further, Applicants do not merely claim an amino acid sequence with seven specific amino acid residues. Rather Applicants claim a reverse transcriptase, and at that, a bacterial RT. Such bacterial RTs have structural features in common which distinguish

them from other polypeptides. Thus this is a limited genus of compounds which applicant claims. One skilled in the art would recognize the structural features of the claimed RTs.

Rejections Under 35 U.S.C. §102

Claims 1, 2, 5, 6, 8, 10, 15 and 16 have been rejected under 35 U.S.C. §102(b) as being anticipated by Lim and Mas (Cell, 56: 89-904, 1989). Applicants respectfully traverse this rejection and assert that the Lim and Mas reference fail to teach or suggest the presence of a 485 amino acid open reading frame, which is now recited in Claim 1. Applicants respectfully submit that the Lim and Mas reference disclose an open reading frame that is 320 amino acids in length. The Applicants, however, have shown an open reading frame of 485 amino acids. Clearly, this significant residue number disparity will lead to structural and functional variations between the Applicants RT and the RT taught by Lim and Mas.

The Examiner has asserted that the amino acid sequence of the Applicants' invention would be **an inherent property** of the bacterial reverse transcriptase as taught by Lim and Mas. We kindly ask the Examiner to consider the case of *Continental Can Co. USA v. Monsanto Co.,* 20 U.S.P.Q. 2d 1744,1746 (Fed. Cir. 1991). The Court in *Continental Can Co.,* held that where a reference is silent about an asserted inherent characteristic, such a gap in the reference may be filled in and proved by extrinsic evidence. However, such evidence must make clear that the missing descriptive matter is necessarily present in the inherent property described in the

reference. Clearly, the Lim and Mas statement that "ORF 320 is required for the production of msDNA *in vivo*" (Lim and Mas. p. 902, col. 1) shows that the inherent property (the amino acid sequence could not be present in the reverse transcriptase taught by the Lim and Mas reference. Further, the Lim and Mas reference, to which the Applicants refer to on page 15 of their specification, merely teaches that the gene for reverse transcriptase is somehow linked to the msDNA region.

The Court, in *Ethel Molded Product Co., v. Betz Package, Inc.* 9 U.S.P.Q. (Ed. Ky. 1988), declared that "the doctrine of inherency is available only when the prior event can be established as a certainty."

In light of the above, Applicants respectfully assert that the Lim and Mas reference fails to anticipate the amended claims of the Applicants invention.

§103 Rejections

Applicants traverse the Examiner's apparent rejection that the §1.131 Declaration is insufficient for failing to show factual support for the prior reduction to practice. Nevertheless, Applicants respectfully submit that Claims 1, 2, 4-8 and 15-17 are clearly patentable over either of Inouye et al. (U.S. 5,320,958 or U.S. 5,434,070), in view of the combination of Rice et al. (July 1993), Xiong et al. (1990) and Hsu et al. (April 1992). Applicants respectfully submit that the combination is a hindsight construction that uses an "obvious to try" standard.

The Examiner is asked to consider the June 4, 1998 Office Action, wherein the Examiner asserted, in a §103 rejection, that it would have been "obvious to isolate and

purify" the existing RTs from any of the sources and sources known to contain RTs. Since that rejection the Examiner has continued to use much of the same reasoning in subsequent §103 rejections. Applicants respectfully submit that these assertions are "obvious to try" assertions, rather than an obviousness rejection.

Rice et al. refers to the highly diverse nature of msDNA producing retroelements in rhizobial strains. This highly diverse nature in rhizobial strains makes isolation and purification of these retroelements difficult and unpredictable. Specifically, page 4251 of Rice et al. points out that each of the bacterial groups appears to have its own unique groups of retroelements with little similarity among retroelements. Rice et al. also reported that there was no cross-hybridization with the foreknown *E.coli* retrons (Ec 67, Ec 86, Ec 73 and Ec 107) or the two microbacterial retrons (Mx 65 and Mx 162). Rice et al. further illustrates the difficulty of isolating and purifying reverse transcriptases by reporting that various bacterial family members appear to contain only a few retron containing strains among the populations sampled. Finally, Rice et al. suggests that retron elements are mobile elements (page 4253) and, as a result, Applicants submit that it would necessarily be difficult to isolate and purify reverse transcriptases from mobile retron elements.

Given the mobility, small percentage of strains of bacteria containing the retrons, diverse nature of retron elements among strains, and the lack of an ordinary cross hybridization signal, Applicants submit that the diverse behavior of retrons makes the isolation and purification of reverse transcriptases only "obvious to try".

The Examiner is asked to consider Xiong et al. where it is reported that analysis of RT sequences has been conducted by Doolittle and co-workers (Doolittle et al. 1989), with somewhat different conclusions, than the results reached by others in the field (Xiong et al., page 3353). The Examiner is further asked to consider the case of *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 13 U.S.P.Q. 2d (D. Mas. 1989), Judgment aff'd in part, vacated in part on other grounds, 18 U.S.P.Q. 2d 1014,1016 (Fed. Cir.1991). In *Amgen*, the Federal Circuit noted that an "obvious to try" standard did not offer a reasonable expectation of success for the Applicant. In coming to its conclusion, the Federal Circuit stated that simply because the overall homology of baboon DNA and human DNA was roughly 90%, it was only "obvious to try" the monkey probe. *Amgen, Inc.* 13 U.S.P.Q. 2d at 1018. Realization of the successful use of the monkey probe would not necessarily have been obvious. *Id.* The Court noted that there are many pitfalls in probing and isolating sequences. *Amgen Inc.*, 18 U.S.P.Q. 2d at1022-1023.

In a case of particular interest, *In re Vaeck* assessed the patentability of an invention relating to a genetically engineered insecticide. *In re Vaeck*, U.S.P.Q. 2d, 1438 (Fed. Cir. 1991). Of interest, the Court opined that while several references disclosed homologies between bacteria and cyanobacterial, these same references taught differences as well as similarities. In applying the principal of *In re Vaeck*, the differences in retrons as described in Rice et al., and pointed out in this response, clearly show no suggestion, implicit or explicit, that there would be a reasonable expectation of success of isolating and purifying reverse transcriptases from the highly

diverse retrons of a number of bacterial species. Whether a particular combination might be "obvious to try" is not a legitimate test for patentability.

Turning now to the rejection of Claims 1, 2, 4-6, 8, 10, 15-17 as rejected as being unpatentable over Hsu et al. as applied to Claims 1, 2, 4-8 and 15-17, and further in view of Lim and Mass, Applicants respectfully submit that contrary to the Examiner's assertion in the last Office Action, dated July 8, 2002, the introduction/abstract of Hsu et al. **does not** discuss the homologies of msDNA from *mZantas* and *E.coli*. Rather, Hsu et al. discuss similarity between *mZantas* and *Aurantiaca* and point out that the high identity "between the two RTs is unique among all other known bacterial RTs which do not share more than 40% identities." (Hsu et al., page 2385). Accordingly, the teaching of Hsu et al. illustrate, once again, the high diversity of RTs among bacterial species.

In light of the foregoing, Applicants respectfully submit that the entire Application is now in condition for allowance, which action is respectfully requested.

Respectfully submitted,

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